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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/341,590	07/13/99	LARSEN B	PPI-20479-US

HM22/0905

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EXAMINER	
LUKTON, D	

ART UNIT	PAPER NUMBER
1653	24

DATE MAILED: 09/05/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/341,590	Due Larsen
Examiner	**Art Unit**
David Lukton	1653

-- The MAILING DATE of this communication appears on the cover sh et with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jun 11, 2001*

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-32, 37, and 52-68* is/are pending in the applica

4a) Of the above, claim(s) _____ is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1-32, 37, and 52-68* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Pursuant to the directives of paper No. 22 (filed 6/11/01), claims 1 6 9 10 21 23 37 have been amended, claims 39, 41, 43, 45, 47, 49 cancelled, and claims 52-68 added.

Claims 1-32, 37, 52-68 are pending.

As indicated previously, none of claims 3-5, 13-18, 21-23, 27, 28 encompasses the elected specie. While none of these claims is withdrawn from consideration at the present time, these claims may be withdrawn at a later time.

Applicants' arguments filed 6/11/01 have been considered and found persuasive in part. The rejection of claims 1-3 over Larsen (WO 98/11126) is withdrawn.

*

A substitute specification is required. Applicants have requested numerous amendments to the specification. These are too numerous for entry. Accordingly, A substitute specification is required.

*

This application contains sequence disclosures that are encompassed by the definitions for amino acid sequences set forth in 37 CFR 1.821. However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 with regard to the sequence disclosures.

As indicated previously, further sequence listings are required. The claims encompass conjugates in which "X" can be any of the following:

enkephalin, Leu-enkephalin, Met-enkephalin, endothelin, vasoactive intestinal peptide, substance P, neurotensin, endorphin, insulin, gramicidin, paracelsin, delta-sleep inducing peptide, angiotensin-I, angiotensin-II, angiotensinogen, angiotensinogen, vasopressin, oxytocin, calcitonin, calcitonin gene-related peptide, calcitonin gene-related peptide-II, parathyroid hormone (1-34), parathyroid hormone related peptide, EMP-1, atrial natriuretic peptide, brain natriuretic peptide, C-type natriuretic peptide (1-53), "mini-ANP", cecropin, kinetensin, neurophysins, elafin, guamerin, atriopeptin-I, atriopeptin-II, atriopeptin-III, deltorphin-I, deltorphin-II, vasotocin, bradykinin, dynorphin, dynorphin-A dynorphin-B, GRH, GH releasing factor, GH releasing peptide, growth hormone, tachykinin, ACTH, cholecystokinin, corticotropin releasing factor, diazepam binding inhibitor fragment, FMRF-amide, leupeptin, sandostatin, galanin, gastric releasing peptide, gastric inhibiting polypeptide, glucagon, glucagon-like peptide -1, glucagon-like peptide-2, exendin-3, exendin-4, LHRH, melanin concentrating hormone, melanocyte stimulating hormone, alpha-MSH, morphine modulating peptide, somatostatin, substance K, TRH, Kyotorphin, melanostatin, hirulog, hirulog-1, melanotan-II, thymosin alpha-1, ornipressin, octreotide, motilin, neurokinin-A, neurokinin-B, neuromedin B, neuromedin C, neuromedin K, neuromedin N, neuromedin U, neuropeptide K, neuropeptide Y, PACAP, pancreatic polypeptide, peptide YY, peptide histidine methionine amide, secretin, thrombopoetein, insulin-like growth factor-I, insulin-like growth factor II, GHRP-6, interleukin-II, beta-interleukin-I, beta-interleukin-II, epidermal growth factor (20-31), eptifibatide, endomorphin-1, endomorphin-2, adrenomodulin, antiarrhytmic peptide, antagonist G, indolicin, osteocalcin, cortistatin-29, cortistatin-14, PD-145065, PD-142893, fibrinogen binding inhibitor peptide, leptin 93-105, GR 83074, and Tyr-W-MIF-1.

A sequence listing has been provided for many of these; however, applicants have failed to provide a sequence listing for all of them. A sequence listing is required for each of the foregoing peptides (that has not already been provided). The sequence listing will aid in the search.

Applicants have argued that they should not be required to submit the sequences. The primary issue pertains to the following phrase in one or more of the claims:

"or a modified or **truncated fragment** thereof".

Thus, for example, a search would have to be undertaken not only for every peptide in claim 68, but for every fragment of every peptide which might be bonded to a "Z" moiety. In order to conduct such a search for all possible fragments, the sequences of every peptide (from which the fragments are derived) must be set forth. It would be possible, given

enough time and effort, for the examiner to find references that disclose each of the (non-fragmented, "parent") peptides. However, this would impose an undue burden on the examiner, who would then have to search every possible fragment of those sequences. It is suggested that the phrase at issue be deleted ("a truncated fragment thereof"). If this is deleted, the sequence requirement will be reconsidered. Otherwise, it is suggested that applicants begin supplying all sequences. Failure to do so may indeed result in abandonment. In the event of abandonment, a decision will be made by another authority as to the appropriate burden on the examiner *versus* the applicant.

Applicant is given the time period set in this letter within which to comply with the sequence rules, 37 CFR 1.821-1.825. Failure to comply with these requirements will result in ABANDONMENT of the application under 37 CFR 1.821(g). Extensions of time may be obtained by filing a petition accompanied by the extension fee under the provisions of 37 CFR 1.136. In no case may an applicant extend the period for response beyond the six month statutory period.

*

The elected specie is Leu-enkephalin-$(Lys)_6$. As stated by applicants, claims 1, 2, 6-12, 19, 20, 24-26, 29-32, 37 encompass the elected specie, and claims 3-5, 13-18, 21-23, 27, 28 do not. At the present time, none of claims 3-5, 13-18, 21-23, 27, 28 is withdrawn from consideration. However, those claims which do not encompass the elected specie *may be withdrawn* at a later time.

Claims 1-32, 37, 52-68 are examined in this Office action.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 37 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claim 37 is drawn to a method of inhibiting neurons from transmitting pain impulses to the spinal cord. However, there is no evidence that this is the case. Applicants have argued only that the claimed invention is "described". That there exists an assertion in the specification that the claimed compounds can inhibit neurons from transmitting pain impulses to the spinal cord is not challenged. Description *per se* is not the issue. The fact is that there is no evidence that even one of the claimed compounds has any effect one way or another on any neuronal cells. Moreover, there are neuronal cells throughout the body; even if it were true that it were possible to inhibit the neurotransmission between nerves in e.g., the hand and neurons in the spinal cord, why would one expect to inhibit neurotransmission between nerve cells in the brain and neurons in the spinal chord? And on what basis are applicants asserting that only the transmission "pain" impulses is inhibited; what about the sensations of temperature changes, and merely (non-painful) touch...? Why are these not inhibited as well?

As it happens, one cannot merely select compounds at random, and select mechanisms of

action at random and hope to achieve any degree of success. Obtaining pharmacologically useful compounds is difficult enough when a rational approach is followed, and when at least *in vitro* data is obtained. But when the compounds and processes are selected entirely at random, there is no chance of obtaining any efficacy at all.

Even the expenditure of "undue experimentation" is unlikely to yield useful data.

*

Claims 1-32, 37, 52-68 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- Claim 1 recites (last line) "at least about 2". This renders the claim indefinite as to the lower limit. Is the lower limit 2, or is the lower limit less than 2...? It is suggested that the "about" qualifier be deleted. This rejection applies to all claims reciting the phrase "at least about", or "consists of at the most about".

- Claim 1 recites a definition for variables R1 and R2. Within that definition is the following phrase:

  "e.g., 2, 4-diaminobutanoic acid and 2, 3-diaminopropanoic acid"

  This constitutes improper Markush format. It is suggested that the phrase at issue be deleted and moved to a dependent claim.

- Claim 1 recites the phraes "covalently bound". However, this term is somewhat indefinite. The term "bound" is broader than "bonded"; for example, the term "bound" would encompass a loose association between two molecules, for example. Accordingly, to the extent that the term "bound" encompasses more than "bonded", the claim is indefinite. It is suggested that the claim recite *covalently bonded.*

- Claim 3 is not properly subgeneric to claim 1. Claim 3 should be cancelled, or

written in independent form.

- In claim 4, the phrase "the first sequence" and "the second sequence" both lack antecedent basis.

- Claim 5 is not properly subgeneric to claim 1. Claim 5 should be cancelled, or written in independent form.

- Claim 29 is indefinite as to the process steps. How is the nucleic acid sequence introduced? Is it sufficient to merely combine a polynucleotide with the host cell, or is a vector, such as a plasmid, required? Is a promotor required...? Is the peptide conjugate produced as such, or is a cleavage step required? As for step (b), the following should be recited:

  culturing said host cell for a time and under conditions effective to produce said peptide conjugate.

- Claim 29 is indefinite as to the process steps. Assuming that one can introduce the appropriate polynucleotide into the host cell, how is the peptide cleaved, or is it applicants position that the target peptide is produced as such, i.e., not part of a larger peptide?

- In claim 19, "Xaa" is undefined in many of the sequences.

- Claim 54 recites, on the one hand, that "Z" consists of 4-20 amino acids (line 4), but at the same time, that "Z" consists of 4-10 amino acids (last line of claim). Thus, which is it?

- Claim 62 mandates (last line) that "Z" is $(Dbu)_n$ or $(Dpr)_n$, but earlier in the claim is defined much more broadly. What is the definition of "Z" in this claim??

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2) and (4) of section 371(c) of this title before the invention thereof by the applicant for the patent.

Claims 1-2, 19, 24, 52-57, 62, 64-68 are rejected under 35 U.S.C. §102(b) as being anticipated by Neer.

As indicated previously, Neer teaches col 2, line 4+ that the first 26 amino acids of the peptide set forth in col 4, line 60+ are "active". As indicated (col 4, line 60+), the amino acid sequence at positions 20-34 is the following:

RVEWLRKKLQDVHNF

Thus, the PTH(1-34) can be viewed as a "conjugate" between PTH(1-26) and the peptide "KLQDVHNF". In traversing, applicants have argued the following:

(a) the cited "Z" sequence is "within" a PTH peptide; this possibility is precluded by claim 1;

(b) claim 1 mandates that "Z" have a free carboxyl at its C-terminus, the prior peptide does not meet this limitation; and

(c) in claim 1, the "Z" peptide must be bonded to the C-terminus of "X", and this limitation is not met by the prior art peptide.

As it happens, applicants are incorrect on all three points. As for the first point, it is true

that the cited "Z" sequence is "within" a PTH peptide; however, claim 1 is drawn to a peptide "comprising" Z and X. The term "comprising" means that, at a minimum, the C- and N-terminii are optionally substituted with amino acids, peptides, or anything else. (While it is not yet an issue, the term "comprises" would also encompass further modifications at any side chain). Thus, claim 1 does encompass a peptide in which "Z" is "within" a peptide. As for the second point, there is no requirement, or even a suggestion in any of the independent claims that "Z" have a free carboxyl at its C-terminus. In re-asserting this point, applicants should identify the exact phrase in claim 1 which they believe mandates this. As for the third point, it is true that the "Z" peptide must be bonded to the C-terminus of "X"; however, this limitation is met by the prior art peptide.

Claim 68 is encompassed because of the phrase "or a modified or truncated fragment thereof"

The rejection is maintained.

*

Claim 5 is rejected under 35 U.S.C. §102(b) as being anticipated by Katz (USP 5,716,614) or Ryser USP 4,847,240.

Katz and Ryser both teach conjugates of polylysine and biologically active peptides.

Thus, the claim is anticipated.

*

Claims 1-2, 19, 24, 52-57, 62, 64-68 are rejected under 35 U.S.C. §102(b) as being

anticipated by Docherty (*Antimicrob Agents Chemother* 31, 1562, 1987) or Burger (*J. Biol. Chem.* **193**, 13, 1951)

Each of Docherty and Burger teach that polylysine exhibits antiviral properties. The references teach that, while the efficacy may be dependent on the chain length, the efficacy can be observed in a variety of chain lengths. Accordingly, polylysine can be viewed as a "conjugate" between one polylysine and another, i.e., $(Lys)_n$ can be viewed as a "conjugate" between $(Lys)_m$ and $(Lys)_p$, wherein n, m and p are integers, and wherein "n" is equal to the sum of "m" and "p".

Thus, the claims are anticipated. (Claim 68 is encompassed because of the phrase "or a modified or truncated fragment thereof").

*

Claims 1 and 68 are rejected under 35 U.S.C. §102(b) as being anticipated by Sumner-Smith (USP 5,646,120).

Sumner-Smith teaches that poly-arginine inhibits HIV replication. See, for example, col 6, line 15-20 for examples. Thus, $(Arg)_n$ can be viewed as a "conjugate" between $(Arg)_m$ and $(Arg)_p$, wherein n, m and p are integers, and wherein "n" is equal to the sum of "m" and "p".

Thus, the claim is anticipated. (Claim 68 is encompassed because of the phrase "or a modified or truncated fragment thereof").

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton [phone number (703)308-3213].

An inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1800